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EP-A- 0 209 707
EP-A- 0 312 004
US-A- 4 243 806

CHEMICAL ABSTRACTS, vol. 69, no. 17, 21st October 1968, page 6075, column 2,abstract no. 65106g, Columbus, Ohio, US; K.H. KOEHLER et al.:

the Amaranthus cytokinin test. III. Benzimidazoles and other compounds",& FLORA (JENA), ABT. A 1968, 159, 293-8

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CHEMICAL ABSTRACTS, vol. 108, no. 1, 4th January 1988, page 5911, abstract no.5914J, Columbus, Ohio, US; V.A. KUZNETSOV et al.: "Derivatives of 5(6)-aminobenzimidazole", & ZH. ORG. KHIM. 1987,23(3), 637-42

CHEMICAL ABSTRACTS, vol. 110, no. 21, 22nd May 1989, page 739, abstract no.192707v, Columbus, Ohio, US; I.V. SKLYAROVA et al.: "Synthesis and biologicalactivity of 5(6)-amido-and 5(6)-amino-2-arylbenzoimidazole derivatives",& KHIM.-FARM. ZH. 1988, 22(6), 697-9

CHEMICAL ABSTRACTS, vol. 107, n. 20, 16th November 1987, page 755, abstract no.187218v, Columbus, Ohio, US; & JP-A-62 55 644 (KONISHIROKU PHOTO INDUSTRY CO., LTD) 11-03-1987

CHEMICAL ABSTRACTS, vol. 107, no. 14, 5th October 1987, page 582, abstract no.124494m, Columbus, Ohio, US; & JP-A-62 50 751 (KONISHIROKU PHOTO INDUSTRY CO., LTD) 05-03-1987

CHEMICAL ABSTRACTS, vol. 107, no. 14, 5th October 1987, page 580, abstract no.124477h, Columbus, Ohio, US; & JP-A-62 24 244 (KONSHIROKU PHOTO INDUSTRY CO., LTD) 02-02-1987

CHEMICAL ABSTRACTS, vol. 84, no. 11, 15th March 1976, page 29, abstract no.69388j, Columbus, Ohio, US; W.C. CAMPBELL et al.: "Effect of parenterallyinjected benzimidazole compounds on Echinococcus multilocularis and Taeniacrassiceps metacestodes in laboratory animals", &J. PARASITOL. 1975, 61(5), 844-52

CHEMICAL ABSTRACTS, vol. 72, no. 17, 27th April 1970, page 399, column 1,abstract no. 90461q, Columbus, Ohio, US; &ZA-A-68 00 351 (MERCK AND CO., INC.) 17-07-1969

Kuznetsov et al., Zhurnal Organicheskoi Khimii, March 1987, Vol. 23 (3), pp. 637-642 (English translation)

Description

This invention relates to novel benzimidazole compounds and their use. The new compounds of the present invention are inhibitors of both the cycloooxygenase (CO) and lipoxygenase (LO) enzymes, and are of use in the treatment or alleviation of allergic or inflammatory conditions in mammals including humans.

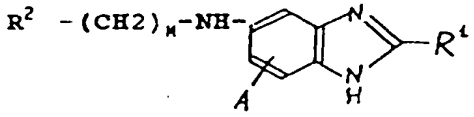
Arachidonic acid is known to be the biological precursor of several groups of endogenous metabolites, prostaglandins including prostacyclins, thromboxanes and leukotrienes. The first step of the arachidonic acid metabolism is the release of esterified arachidonic acid and related unsaturated fatty acids from membrane phospholipids, via the action of phospholipase. Free fatty acids are then metabolized either by cyclooxygenase to produce the prostaglandins and thromboxanes or by lipoxygenase to generate hydroperoxy fatty acids which may be further converted to the leukotrienes. The prostaglandins exhibit diverse physiological effects depending upon their structure. For example, PGE and PGA inhibit gastric secretion as well as lower arterial blood pressure. The thromboxane, especially, thromboxane A2 is a potent vasoconstrictor and platelet aggregatory substance. The leukotrienes are the biological source of the slow reacting substance of anaphylaxis (SRS-A), a chemical mediator in allergic bronchial asthma.

Aspirin and most other non-steroidal antiinflammatory drugs inhibit the cyclooxygenase enzyme. Both antiinflammatory activity and analgesic activity are associated with inhibition of the action of cyclooxygenase. The lipoxygenase inhibiting activity of one agent, AA861 [2,3,5-trimethyl-6-(12-hydroxy-5,10-cyclodecadiynyl)-1,4-benzoquinone], has been reported [see, Yoshimoto et al., Biochem, et Biophys. 713, 470-473 (1982)]. CGS-5391B [(C. E. Hock et al., Prostaglandins, 28, 557-571(1984)] has recently become known as a combined cycloxygenase and lipoxygenase inhibitor.

PCT Patent Application PCT/JP84/00452 (WO 85/01289) and Japanese patent publication No. 107958/1988 describe and claim a number of benzoxazolone and benzothiazolone derivatives useful for the treatment of inflammatory conditions and thrombosis.

Koehler & Conrad (Flora (Jena) Abt. A. 1968, 159, 293-298 and Kuznetsov, Garabsdzhui and Ginzburg (Zh. Org. Khim. 1987, 23(3), 637-42) describe certain benzimidazoles including some substituted by benzylamine or furfurylamino groups.

The present application provides benzimidazole compounds capable of inhibiting both cyclooxygenase and lipoxygenase having the formula



(I)

and the pharmaceutically acceptable salts thereof,
wherein

R^1 is $-NHR^3$, $-NR^3$(loweralkyl) or R^4;

R^2 is phenyl, substituted phenyl, naphthyl or cyclohexyl wherein the substituents on said substituted phenyl are selected from the group consisting of lower alkyl, lower alkoxy and halo;

R^3 is lower alkyl, phenyl, substituted phenyl or naphthyl; wherein the substituents on said substituted phenyl are selected from the group consisting of lower alkyl, lower alkoxy and halo;

R^4 is phenyl, substituted phenyl, naphthyl or cyclohexyl; wherein the substituents on said substituted phenyl are selected from the group consisting of lower alkyl, lower alkoxy and halo;

A is hydrogen or halo; and

m is an integer of 1 to 3.

In the above formula, the term "loweralkyl" in R^3 means an alkyl group having 1 to 3 carbons. The term "lower alkoxy" means an alkoxy group having 1 to 5 carbons, preferably up to 2 carbon atoms.

The term "halo" means fluorine, chlorine, bromine or iodine.

The pharmaceutically acceptable salts of the compounds of the formula (I) are those formed from acids which form non-toxic sulfate or bisulfate, phosphate, acetate, citrate, fumarate, gluconate, lactate, maleate, succinate, tartrate, methanesulfonate, benzene sulfonate and toluenesulfonate, formate salts.

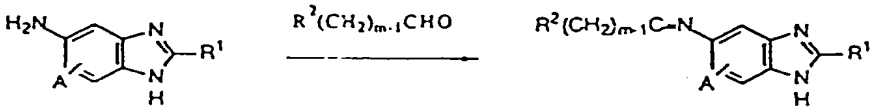
Among the especially preferred individual compounds of the present invention are:
5-(3-phenylpropyl)amino-2-(o-tolyl) benzimidazole, dihydrochloride;
2-anilino-5-benzylamino benzimidazole, dihydrochloride;
5-benzylamino-2-propylamino benzimidazole, dihydrochloride;

5-benzylamino-2-(o-toluidino) benzimidazole, dihydrochloride;
5-benzylamino-2-(p-butylanilino) benzimidazole, dihydrochloride;
5-benzylamino-2-(α-naphthyl)amino benzimidazole, dihydrochloride;
and
2-[(N-methyl)anilino]-5-benzylamino benzimidazole.

The present invention also includes a pharmaceutical composition comprising a pharmaceutical acceptable carrier or diluent and a compound of formula (I).

Also embraced by the present invention is a use of a compound of formula (I) for making a medicament for inhibiting the action of the lipoxygenese as well as the action of the cyclooxygenase.

The compounds of formula (I) may be prepared by a number of different routes. In one embodiment, they are prepared from an amino-substituted compound of the formula (II) according to the following reaction steps:



(II) (III)

(I)

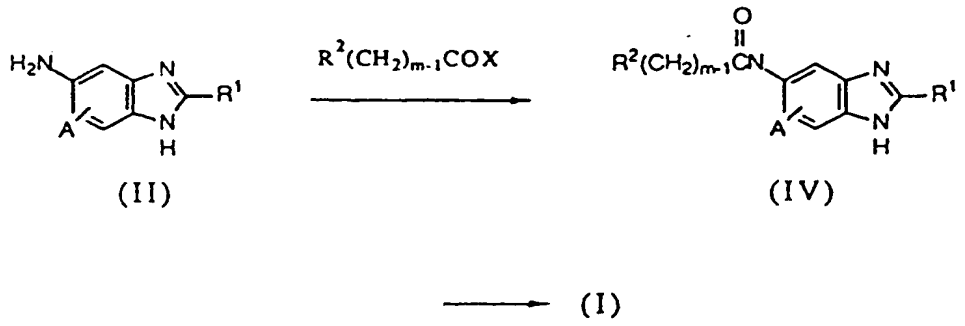
In the above formulae, R^1, R^2, m and A are as previously defined. The first step involves the treatment of compound (II) with an aldehyde, $R^2(CH_2)_{m-1}CHO$, in the presence of a dehydrating agent. The reaction is preferably conducted at ambient temperature. Higher temperatures up to 80 °C can be employed without any significant disadvantage. Suitable solvents which do not react with the reactants and/or products are, for example, benzene, toluene, ethanol and tetrahyrofuran. The preferred dehydrating agent is molecular sieves, although inorganic salts such as magnesium sulfate and sodium sulfate can also be employed. When the preferred temperature is used, the reaction is substantially complete within a few hours. On completion, the product (III) can be isolated and/or purified conventionally, e,g, recrystallization or chromatography. It is, however, more convenient not to isolate this product but to subject it (i.e. in situ) to reaction conditions of the second step.

The starting materials (II) and the aldehyde $R^2(CH_2)_{m-1}CHO$ are either known compounds or may be prepared by methods reported in the art references, see e.g., D. G. Bapat and M. V. Shirsat, **Indian J. Chem.**, 3(2), 81 1965, and J. Garin, E. Melendez, F. L. Merchan, C. Tejel and T. Tejero, **Synthetic Commun.**,375 **1983.**

The second step involves reduction of the C = N double bond by reaction with an appropriate hydrogen source. For example, compounds (III) may be reduced catalytically with hydrogen. It is normally achieved with a heterogeneous catalyst such as platinum (PtO_2), palladium (Pd/C) or nickel in e.g. methanol or ethanol at ambient temperature. Heating is possible but is not generally necessary.

Alternatively, the compounds may be reduced using a metal hydride. The hydride agents suitably employed in this reduction include sodium borohydride, sodium cyanoborohydride and lithium cyanoborohydride. This reaction is conducted at ambient temperature, with an excess of the hydride agent in e.g methanol or ethanol. A similar reduction using stannous chloride acid agent as a reducing agent can be carried out in methanol/aqueous hydrochloric acid. A preferred temperature for carrying out this is from 0 °C to 80 °C. Reduction is ordinarily complete within a few hours. The product of formula (I) is isolated by standard methods known in the art. Purification can be achieved by conventional means, such as recrystallization or chromatography.

In another embodiment, the compounds of formula (I) are prepared by the following process:



In the above formulae, R^1, R^2, m and A are as previously defined and X is an easy leaving group.

The amide (IV) is prepared by standard methods known in the art. For example, the amine (II) is reacted with an activated acid (known to those skilled in the art) such as an acid chloride, acid anhydride or activated carboxylic acid (e.g. imidazoyl derivative) in a reaction-inert solvent either in the presence or absence of a base. A wide variety of bases can be used in the reaction and they include organic amines, alkali metal hydroxides, alkaline metal corbonates, alkaline metal hydrocarbonates, alkaline earth metal hydrides and alkaline earth metal alkoxides. Preferred basic agents are triethylamine, pyridine, sodium hydroxide, potassium tert-butoxide, sodium hydride, potassium carbonate and sodium carbonate. Suitable reaction-inert solvents include methylene chloride, tetrahydrofuran, benzene, toluene, xylene and water. The reaction is usually carried out in the temperature range of 0 C to the boiling point of the solvent. Reaction times of from 30 minutes to a few hours are common. The product can be isolated and purified by conventional procedures, such as recrystallization or chromatography.

The second step usually involves reduction of the amide bond with an appropriate metal hydride. The hydride agents suitably employed in this reduction include lithium aluminum hydride, magnesium aluminum hydride, lithium trimethoxyaluminohydride, sodium bis(2-methoxyethoxy) aluminum hydride, alane and borane preferably in tetrahydrofuran, although ether or dimethoxyethane may be employed. Reaction temperature is usually 0 C through to reflux. The product of formula (I) is isolated by standard methods and purification can be achieved by conventional means, such as recrystallization or chromatography.

The pharmaceutically acceptable salts of the novel compounds of formula (I) are readily prepared by contacting said compound wth a stoichiometric amount of an appropriate mineral or organic acid in either an aqueous solution or a suitable organic solvent. The salt may then be obtained by precipitation or by evaporation of the solvent. Among those salts enumerated earlier, an especially preferred salt is the hydrochloride.

The compounds of formula (I) possess inhibiting activity on the action of the cyclooxygenase as well as on the action of the lipoxygenase. This activity has been demonstrated by a cell culture assay using rat peritoneal cavity resident cells which determines the effect of said compounds on the metabolism of arachidonic acid.

The ability of the compounds of formula (I) to inhibit both enzymes make them useful for controlling the symptoms induced by the endogenous metabolites arising from arachidonic acid in a mammalian subject. The compounds are therefore valuable in the prevention and treatment of such disease states in which the accumulation of said arachidonic acid metabolite is the causative factor, e.g., allergic bronchial asthma, skin disorders, rheumatoid arthritis, osteoarthritis, and thrombosis.

Since conventional non-steroidal inflammatory agents such as aspirin only inhibit cyclooxygenase, they suppress inflammatory conditions as well as tend to cause adverse inhibition. Compounds of the present invention, however, are gastrointestinally cytoprotective in addition to possessing anti-allergy and anti-inflammatory activities. Thus, they show less adverse effects and are of value for use as a safe drug.

When a compound of the formula (I) or a pharmaceutically acceptable salt thereof is to be used as either an anti-allergic agent or an anti-inflammatory agent, it can be administered to a human subject either alone, or preferably, in combination with pharmaceutically acceptable carriers or diluents in a pharmaceutical composition, in accordance with stand pharmaceutical practice. A compound can be administered by a variety of conventional routes of administration including oral, parental and by inhalation. When the compounds are administered orally, the dose range will be from 0.1 to 20 mg/kg body weight of the subject

to be treated per day in single or divided doses. If parental administration is desired, then an effective dose will be from 0.1 to 1.0 mg/kg body weight of the subject to be treated per day. In some instance it may be necessary to use dosages outside these limits, since the dosage will necessarily vary according to the age, weight and response of the individual patient as well as the severity of the patient's symptoms and the potency of the particular compound being administered.

For oral administration, the compounds of formula (I) can be administered, for example, in the form of tablets, powders, lozenges, syrups or capsules, or as an aqueous solution or suspension. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch, and lubricating agents, such as magnesium stearate, are commonly added. In the case of capsules, useful diluents are lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents may be added. For intramuscular, intraperitoneal, subcutaneous and intravenous use, sterile solutions of the active ingredient are usually prepared, and the pH of the solutions should be suitably adjusted and buffered.

EXAMPLES

The present invention is illustrated by the following examples. However, it should be understood that the examples are simply illustrative and the invention is not limited to the specific details of these examples. Proton nuclear magnetic resonance spectra (NMR) were measured at 60MHz unless otherwise indicated for solutions in perdeuterodimethyl sulfoxide (DMSO-d_6) and peak positions are expressed in parts per million (ppm) downfield from tetramethylsilane. The peak shapes are denoted as follows: s, singlet,d, doublet; t, triplet; q, quartet; m, multiplet; b, broad.

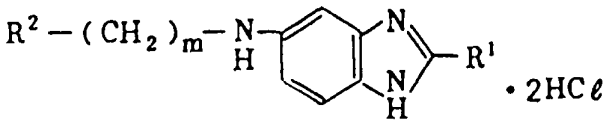
Example 1

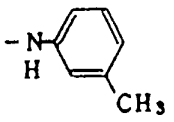
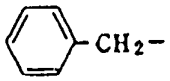
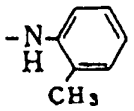
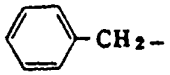
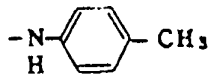
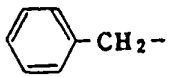
2-Anilino-5-benzylamino benzimidazole dihydrocholoride 5-Amino--2-anilino benzimidazole (4.5 m mol) and benzaldehyde (4.5 m mol) in 15 ml methanol were stirred together for one hour at room temperature. To the reaction mixture was added excess $NaBH_4$ and the reaction mixture stirred a further 30 minutes. The mixture was then concentrated under reduced pressure and resultant residue covered with saturated $NaHCO_3$, extracted into CH_2C1_2 and dried over Na_2SO_4. Pure product was isolated by silica gel column chromatography ($CHC1_3$: CH_3OH = 15 : 1) and the resultant oil covered with HC1-CH_3OH and shaken. The resulting dihydrochloride salt was isolated by filtration to afford 2-anilino-5-benzylamino benzimidazole dihydrochloride in 73% yield.

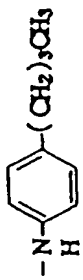
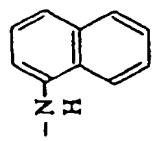
m.p. :	>275 ° C (dec.)
IR (KBr):	3000(br), 1680 cm^{-1}
NMR(DMSO-d_6)S:	11.79 (s, 1H), 7.56-7.20 (m, 13H) 4.47 (s, 2H)

EXAMPLES

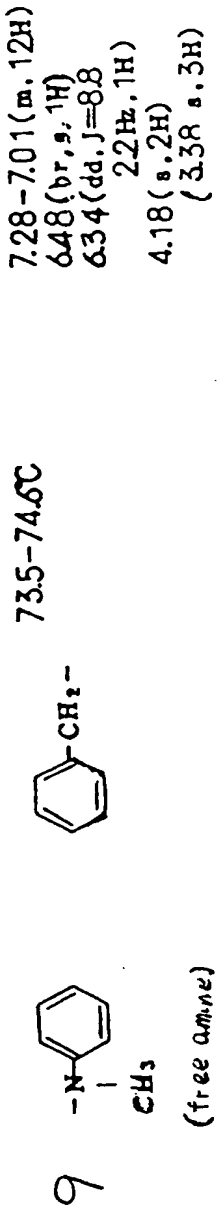
Similarly the following compounds were prepared.



Example No.	R^1	$R^2-(CH_2)_m-$		IR(KBr)	NMR
2.			268-270℃ decomposed	2900(br.), 1660cm^{-1}	11.69(s.1H), 7.5-7.1(m.13H) 4.67(s,2H), 2.36(s, 3H)
3.			232-233.5℃ decomposed	2900(br.), 1670cm^{-1}	7.49-7.24(m.11H), 7.11(br..1H), 4.44(s.2H), 2.29(s.3H)
4.			>270℃ decomposed	3000(br.), 1700cm^{-1}	7.45-7.25(m.12H), 6.95(br..2H), 4.40(s.2H), 2.35(s.3H)

5.		>260℃ decomposed	2900(br.), 1670cm^{-1}	1.135(s,1H) 7.45-7.43(m,3H) 7.36-7.27(m,8H) 7.0(br.2H) 4.40(s,2H) 2.61(t,J=7.3Hz,2H) 1.60-1.55(m,2H) 1.37-1.29(m,2H) 0.91(t,J=7.3Hz,3H)
6.		>235℃ decomposed	2800(br.), 1660cm^{-1}	11.71(s,1H) 8.12-8.02(m,3H) 7.74-7.59(m,4H) 7.47-7.07(m,8H) 4.43(s,2H)

7			205-207℃	3200. 2850. 2700	12.95(br.s.2H) 9.23(s.1H) 7.48(d,J= 5.9 Hz,2H) 7.35-7.32(m.5H) 7.10(d,J=8.8Hz.1H) 4.46(s.2H) 3.39-3.31(m.2H) 1.65-1.57(m.2H) 0.94(t,J=7.3Hz.3H)
8			234-237℃ decomposition	2900. 1660cm^{-1}	11.38(s.1H) 7.45-7.28(m.7H) 7.02-6.85(m.5H) 4.40(s.2H) 3.80(s.3H)



Example 10

5-(3-phenylpropyl) amino-2-phenyl benzimidazole hydrochloride 5-Amino-2-phenyl benzimidazole (19 m mol) and dhydrocinnamoyl chloride (3.12 ml) in 160 ml of benzene were heated at reflux for 3 hours. After cooling the reaction mixture, the resulting precipitate was collected by filtration to afford the hydrochloride salt of the amide in 76% yield.

m.p. :	216.5 – 219.5 • C
IR(KBr):	3350, 2800, 1660 cm^{-1}
NMR(DMSO-d_6)S:	10.45 (s, 1H), 8.41 (s, 1H) 8.35-8.25 (m, 2H), 7.8-7.58 (m, 5H),

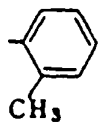
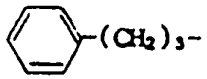
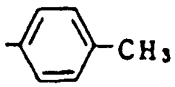
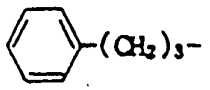
7.3-7.19 (m, 5H),
2.96 (6, J = 7Hz, 2H)
2.71 (6, J = 7Hz, 2H)

To the amide (7m mol) suspended in 50 ml THF was added $LiAlH_4$ (13 m mol) portionwise in solid form. After addition of all the $LiAlH_4$, the reaction mixture was heated at reflux for 5 hours, cooled and worked-up by standard procedure. Free alkyl amine was isolated via column chromatography (silica gel, 25% ethyl acetate in hexane) and shaken with HCl-methanol. The dihydrochloride salt was isolated by filtration to afford product in 59% yield.

m.p. :	243.9 - 245.9 °C
IR(KBr):	3450, 2700 (br.) cm^{-1}
NMR(DMSO-d_6)s:	8.37 (br., 2H), 7.73-7.70(m, 4H) 7.33-7.19(m, 7H), 3.22 (br.,2H) 2.76-2.70(m,2H), 2.05-1.92 (m,2H)

EXAMPLES 11 - 15

Similarly the following compounds were prepared.

Example No.	R^1	$R^2-(CH_2)_m-$		IR(KBr)	NMR
11			233-236℃	3450. 2700cm^{-1}	7.79-7.49(m,5H) 7.30-7.19(m,7H) 3.16(t,J=7.3Hz,2H) 2.73(t,J=7.3Hz,2H) 2.56(s,3H) 2.03-1.90(m,2H)
12			245.8-248.1℃	2500cm^{-1}	8.25(d,J=8.8Hz,2H) 7.70(d,J=8.8Hz,1H) 7.51(d,J=8.1Hz,2H) 7.32-7.19(m,7H) 3.20(t,J=8.06Hz,2H) 2.73(t,J=8.06Hz,2H) 2.44(s,3H) 2.01-1.90(m,2H)

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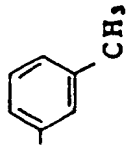
13			>211℃ decomposed	3400. 2750(br.)cm^{-1}	8.23(s,1H) 8.19(d,J=8.8Hz,1H) 7.72(d,J=8.8Hz,1H) 7.64-7.50(m,2H) 7.40-7.12(m,7H) 3.21(t,J=8.1Hz,2H) 2.73(t,J=8.1Hz,2H) 2.45(s,3H) 1.99(m,2H)
14			241.5-242.7℃	3450. 2800(br.)cm^{-1}	7.75(d,J=8.8Hz,1H) 7.58(br.s,1H) 7.42(d,J=8.8Hz,1H) 7.32-7.15(m,5H) 3.25-3.15(m,3H) 2.71(t,J=6.8Hz,2H) 2.15-1.66(m,8H) 1.45-1.20(m,4H)

15

240.6-243.3 ℃

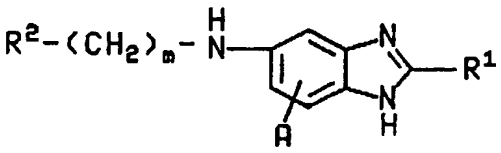
2600(br.)cm^{-1}

8.35(t, J=6.0Hz, 1H)
7.78(d, J=8.8Hz, 2H)
7.63-7.45(m, 3H)
7.50-7.15(m, 6H)
3.22(t, J=6.6Hz, 2H)
2.73(t, J=6.6Hz, 2H)
2.18-1.92(m, 2H)

Claims

Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. A compound of the formula



and the pharmaceutically acceptable salts thereof,
wherein
R^1 is -NHR^3, -NR^3(loweralkyl) or R^4;
R^2 is phenyl, substituted phenyl, naphthyl or cyclohexyl wherein the substituents on said substituted phenyl are selected from the group consisting of lower alkyl, lower alkoxy and halo;
R^3 is lower alkyl, phenyl, substituted phenyl or naphthyl; wherein the substituents on said substituted phenyl are selected from the group consisting of lower alkyl, lower alkoxy and halo;
R^4 is phenyl, substituted phenyl, naphthyl or cyclohexyl; wherein the substituents on said substituted phenyl are selected from the group consisting of lower alkyl, lower alkoxy and halo;
A is hydrogen or halo; and
m is an integer of 1 to 3.

2. A compound according to claim 1
wherein R^1 is -NH-R^3,
R^4 is phenyl which may be substituted or cyclohexyl, and
R^2 is phenyl,

3. A compound according to claim 1
wherein R^1 is -NR^3 (lower alkyl),
R^4 is phenyl which may be substituted and
R^2 is phenyl.

4. A compound according to claim 2 or 3 wherein R^3 and R^4 are phenyl or substituted phenyl and R^2 is phenyl and m is 1.

5. A compound according to claim 1 said compound being
5-(3-phenylpropyl) amino-2- (o-tolyl) benzimidazole, dihydrochloride;
2-anilino-5-benzylamino benzimidazole, dihydrochloride;
5-benzylamino-2-propylamino benzimidazole, dihydrochloride;
5-benzylamino-2- (o-toluidino) benzimidazole, dihydrochloride;
5-benzylamino-2-(p-butylanilino) benzimidazole, dihydrochloride;
5-benzylamino-2-(α-naphthyl) amino benzimidazole, dihydrochloride, or
2-[(N-methyl) anilino]-5-benzylamino benzimidazole.

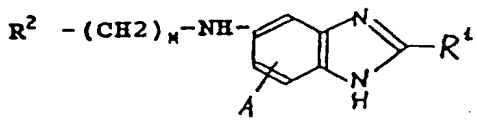
6. A pharmaceutical composition for the treatment of allergic or inflammatory conditions, which comprises a compound of any preceding claim together with a pharmaceutically acceptable carrier.

7. A compound according to any one of claims 1 to 6, for use in medicine.

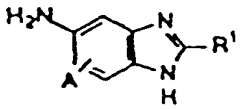
8. Use of a compound according to any one of claims 1 to 6 for making a medicament for inhibiting lipoxygenase or cyclooxygenase.

Claims for the following Contracting States : GR, ES

1. A process for preparing a compound of the formula I



and the pharmaceutically acceptable salts thereof,
wherein
R^1 is $-NHR^3$, $-NR^3$(loweralkyl) or R^4;
R^2 is phenyl, substituted phenyl, naphthyl or cyclohexyl wherein the substituents on said substituted phenyl are selected from the group consisting of lower alkyl, lower alkoxy and halo;
R^3 is lower alkyl, phenyl, substituted phenyl or naphthyl; wherein the substituents on said substituted phenyl are selected from the group consisting of lower alkyl, lower alkoxy and halo;
R^4 is phenyl, substituted phenyl, naphthyl or cyclohexyl; wherein the substituents on said substituted phenyl are selected from the group consisting of lower alkyl, lower alkoxy and halo;
A is hydrogen or halo; and
m is an integer of 1 to 3
characterized by reacting a compound of formula II



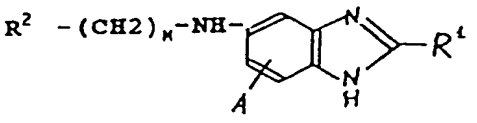
with an aldehyde of formula R^2 $(CH_2)_{m-1}CHO$ wherein A, R_1, R_2 and m are as previously defined followed by reduction of the resultant intermediate to give a compound of the formula I said processes being followed by optional conversion of the product into a pharmaceutically acceptable salt.

2. The process of claim 1 wherein the reaction of the formula II compound and the aldehyde occurs in the presence of a dehydrating agent and the resultant intermediate is either reduced catalytically with hydrogen or reduced with a metal hydride.

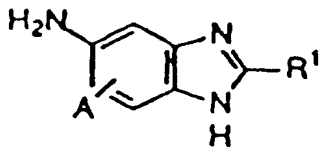
3. The process of claim 2 wherein the reaction of the formula II compound and the aldehyde occurs at a temperature up to 80 °C and the intermediate is reduced catalytically with hydrogen.

4. The process of claim 1 in which
5-(3-phenylpropyl) amino-2- (o-tolyl) benzimidazole dihydrochloride;
2-anilino-5-benzylamino benzimidazole, dihydrochloride;
5-benzylamino-2-propylamino benzimidazole dihydrochloride;
5-benzylamino-2-(o-toluidino) benzimidazole, dihydrochloride,
5-benzylamino-2-(p-butylanilino) benzimidazole, dihydrochloride,
5-benzylamino-2-(α-naphthyl)amino benzimidazole, dihydrochloride, or
2-[(N-methyl) anilino]-5-benzylamino benzimidazole is produced.

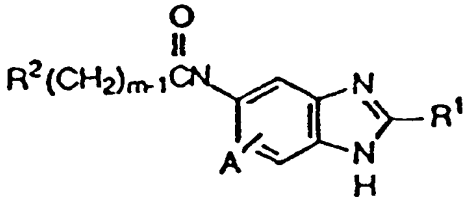
5. A process for preparing a compound of formula I



characterized by: reacting an amide formula II compound



with an activated acid to form an intermediate formula IV compound;



wherein A, R_1, R_2, and m are as previously defined; and reducing the intermediate to give a compound of formula I; said processes being followed by optional conversion of the product into a pharmaceutically acceptable salt.

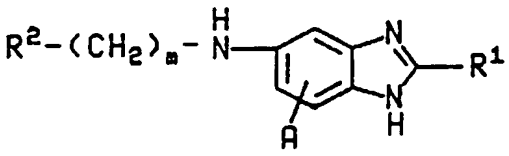
6. The process of claim 5 wherein the reaction of the amide with the activated acid occurs in the presence of a base and the intermediate compound is reduced with a metal hydride.

7. The process of claim 6 wherein the reaction of the amide with the activated acid is carried out at a temperature of 0 • C to reflux and the reduction is carried out at a temperature of 0 • C to reflux.

8. The process of claim 5 in which
5-(3-phenylpropyl)amino-2-(o-tolyl) benzimidazole, dihydrochloride,
2-anilino-5-benzylamino benzimidazole, dihydrochloride,
5-benzylamino-2-propylamino benzimidazole, dihydrochloride,
5-benzylamino-2-(p-butylanilino) benzimidazole, dihydrochloride,
5-benzylamino-2-(o-toluidino) benzimidazole, dihydrochloride,
5-benzylamino-2-(α-naphthyl) amino benzimidazole, dihydrochloride, or
2[(N-methyl) anilino]-5-benzylamino benzimidazole is produced.

Patentansprüche
Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. Verbindung der Formel



und die pharmazeutisch akzeptablen Salze derselben,
worin bedeuten:
R^1 -NHR^3, -NR^3 (Niedrigalkyl) oder R^4;

R^2 Phenyl, substituiertes Phenyl, Naphthyl oder Cyclohexyl, wobei die Substituenten an dem substituierten Phenyl aus der Gruppe Niedrigalkyl, Niedrigalkoxy und Halogen ausgewählt sind;
R^3 Niedrigalkyl, Phenyl, substituiertes Phenyl oder Naphthyl, wobei die Substituenten an dem substituierten Phenyl aus der Gruppe Niedrigalkyl, Niedrigalkoxy und Halogen ausgewählt sind;
R^4 Phenyl, substituiertes Phenyl, Naphthyl oder Cyclohexyl, wobei die Substituenten an dem substituierten Phenyl aus der Gruppe Niedrigalkyl, Niedrigalkoxy und Halogen ausgewählt sind;
A Wasserstoff oder Halogen und
m eine ganze Zahl von 1 bis 3.

2. Verbindung nach Anspruch 1, worin R^1 für -NH-R^3 steht, R^4 gegebenenfalls substituiertes Phenyl oder Cyclohexyl bedeutet und R^2 Phenyl darstellt.

3. Verbindung nach Anspruch 1, wobei R^1 für -NR^3 (Niedrigalkyl) steht, R^4 gegebenenfalls substituiertes Phenyl bedeutet und R^2 Phenyl darstellt.

4. Verbindung nach Anspruch 2 oder 3, wobei R^3 und R^4 für Phenyl oder substituiertes Phenyl stehen, R^2 Phenyl bedeutet und m 1 entspricht.

5. Verbindung nach Anspruch 1, nämlich:
5-(3-Phenylpropyl)amino-2-(o-tolyl)benzimidazol, Dihydrochlorid;
2-Anilino-5-benzylamino-benzimidazol, Dihydrochlorid;
5-Benzylamino-2-propylamino-benzimidazol, Dihydrochlorid;
5-Benzylamino-2-(o-toluidino)benzimidazol, Dihydrochlorid;
5-Benzylamino-2-(p-butylanilino)benzimidazol, Dihydrochlorid;
5-Benzylamino-2-(α-naphthyl)amino-benzimidazol, Dihydrochlorid oder
2-[(N-Methyl)anilino]-5-benzylamino-benzimidazol.

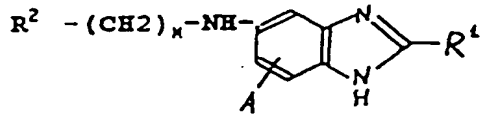
6. Arzneimittelzubereitung zur Behandlung von allergischen Zuständen oder Entzündungszuständen, umfassend eine Verbindung nach einem der vorhergehenden Ansprüche zusammen mit einem pharmazeutisch akzeptablen Träger.

7. Verbindung nach einem der Ansprüche 1 bis 6 zur Verwendung in der Medizin.

8. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 6 zur Herstellung eines Medikaments zur Hemmung von Lipoxygenase oder Cyclooxygenase.

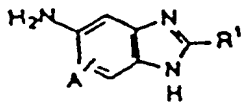
Patentansprüche für folgende Vertragsstaaten : GR, ES

1. Verfahren zur Herstellung einer Verbindung der Formel I



und der pharmazeutisch akzeptablen Salze derselben,
worin bedeuten:
R^1 -NHR^3, -NR^3 (Niedrigalkyl) oder R^4;
R^2 Phenyl, substituiertes Phenyl, Naphthyl oder Cyclohexyl, wobei die Substituenten an dem substituierten Phenyl aus der Gruppe Niedrigalkyl, Niedrigalkoxy und Halogen ausgewählt sind;
R^3 Niedrigalkyl, Phenyl, substituiertes Phenyl oder Naphthyl, wobei die Substituenten an dem substituierten Phenyl aus der Gruppe Niedrigalkyl, Niedrigalkoxy und Halogen ausgewählt sind;
R^4 Phenyl, substituiertes Phenyl, Naphthyl oder Cyclohexyl, wobei die Substituenten an dem substituierten Phenyl aus der Gruppe Niedrigalkyl, Niedrigalkoxy und Halogen ausgewählt sind;
A Wasserstoff oder Halogen und
m eine ganze Zahl von 1 bis 3,

gekennzeichnet durch ein Umsetzen einer Verbindung der Formel II



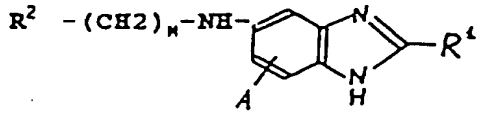
mit einem Aldehyd der Formel R^2 $(CH_2)_{m-1}CHO$, worin A, R_1, R_2 und m die oben angegebene Bedeutung besitzen, und eine anschließende Reduktion des erhaltenen Zwischenprodukts zur Herstellung einer Verbindung der Formel I, wobei diesen Verfahren gegebenenfalls eine Umwandlung des Produkts in ein pharmazeutisch akzeptables Salz folgt.

2. Verfahren nach Anspruch 1, wobei die Umsetzung der Verbindung der Formel II mit dem Aldehyd in Gegenwart eines Dehydratisierungsmittels erfolgt und das erhaltene Zwischenprodukt entweder katalytisch mit Wasserstoff oder mit einem Metallhydrid reduziert wird.

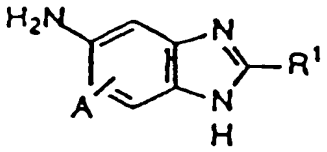
3. Verfahren nach Anspruch 2, wobei die Umsetzung der Verbindung der Formel II mit dem Aldehyd bei einer Temperatur bis zu 80 °C erfolgt und das Zwischenprodukt katalytisch mit Wasserstoff reduziert wird.

4. Verfahren nach Anspruch 1, wobei:
5-(3-Phenylpropyl)amino-2-(o-tolyl)benzimidazol, Dihydrochlorid;
2-Anilino-5-benzylamino-benzimidazol, Dihydrochlorid;
5-Benzylamino-2-propylamino-benzimidazol, Dihydrochlorid;
5-Benzylamino-2-(o-toluidino)benzimidazol, Dihydrochlorid;
5-Benzylamino-2-(p-butylanilino)benzimidazol, Dihydrochlorid;
5-Benzylamino-2-(α-naphthyl)amino-benzimidazol, Dihydrochlorid oder
2-[(N-Methyl)anilino]-5-benzylamino-benzimidazol hergestellt wird.

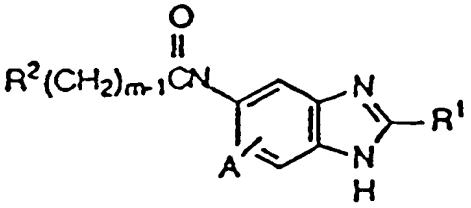
5. Verfahren zur Herstellung einer Verbindung der Formel I



gekennzeichnet durch Umsetzen einer Amidverbindung der Formel II



mit einer aktivierten Säure zur Bildung eines Zwischenprodukts der Formel IV



worin A, R_1, R_2 und m die oben angegebene Bedeutung besitzen, und Reduzieren des Zwischenprodukts zur Bildung einer Verbindung der Formel I, wobei den Verfahren gegebenenfalls eine Umwandlung des Produkts in ein pharmazeutisch akzeptables Salz folgt.

6. Verfahren nach Anspruch 5, wobei die Umsetzung des Amids mit der aktivierten Säure in Gegenwart einer Base erfolgt und die Zwischenproduktverbindung mit einem Metallhydrid reduziert wird.

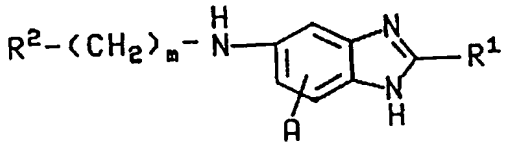
7. Verfahren nach Anspruch 6, wobei die Umsetzung des Amids mit der aktivierten Säure bei einer Temperatur von 0 °C bis Rückflußtemperatur erfolgt und die Reduktion bei einer Temperatur von 0 °C bis Rückflußtemperatur erfolgt.

8. Verfahren nach Anspruch 5, wobei
5-(3-Phenylpropyl)amino-2-(o-tolyl)benzimidazol, Dihydrochlorid;
2-Anilino-5-benzylamino-benzimidazol, Dihydrochlorid;
5-Benzylamino-2-propylamino-benzimidazol, Dihydrochlorid;
5-Benzylamino-2-(p-butylanilino)benzimidazol, Dihydrochlorid;
5-Benzylamino-2-(o-toluidino)benzimidazol, Dihydrochlorid;
5-Benzylamino-2-(α-naphthyl)amino-benzimidazol, Dihydrochlorid oder
2-[(N-Methyl)anilino]-5-benzylamino-benzimidazol gebildet wird.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. Composé de formule



et ses sels pharmaceutiquement acceptables,
formule dans laquelle

- R^1 est un groupe -NHR³, -NR³(alkyle inférieur) ou R⁴ ;
- R^2 est un groupe phényle, phényle substitué, naphtyle ou cyclohexyle, les substituants du groupe phényle substitué étant choisis entre des radicaux alkyle inférieur, alkoxy inférieur et halogéno ;
- R^3 est un groupe alkyle inférieur, phényle, phényle substitué ou naphtyle ; les substituants du groupe phényle substitué sont choisis dans le groupe comprenant des radicaux alkyle inférieur, alkoxy inférieur et halogéno ;
- R^4 est un groupe phényle, phényle substitué, naphtyle ou cyclohexyle ; les substituants du groupe phényle substitué étant choisis dans le groupe comprenant des radicaux alkyle inférieur, alkoxy inférieur et halogéno ;
- A est l'hydrogène ou un radical halogéno ; et
- m est un nombre entier de 1 à 3.

2. Composé suivant la revendication 1, dans lequel R^1 est un groupe -NH-R^3,
R^4 est un groupe phényle qui peut être substitué ou un groupe cyclohexyle,
et
R^2 est un groupe phényle.

3. Composé suivant la revendication 1, dans lequel R^1 est un groupe -NR^3 (alkyle inférieur),
R^4 est un groupe phényle qui peut être substitué
et
R^2 est un groupe phényle.

4. Composé suivant la revendication 2 ou 3, dans lequel R^3 et R^4 sont des groupes phényle ou phényle substitué et
R^2 est un groupe phényle, et m a la valeur 1.

5. Composé suivant la revendication 1, qui est
le dichlorhydrate de 5-(3-phénylpropyl)-amino-2-(o-tolyl)-benzimidazole ;
le dichlorhydrate de 2-anilino-5-benzylamino-benzimidazole ;
le dichlorhydrate de 5-benzylamino-2-propylamino-benzimidazole ;
le dichlorhydrate de 5-benzylamino-2-(o-toluidino)-benzimidazole ;
le dichlorhydrate de 5-benzylamino-2-(p-butyl-anilino)-benzimidazole ;
le dichlorhydrate de 5-benzylamino-2-(α-naphtyl)-amino-benzimidazole ; ou
le 2-[(N-méthyl)-anilino]-5-benzylamino-benzimidazole.

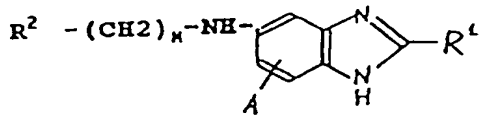
6. Composition pharmaceutique destinée au traitement d'états allergiques ou inflammatoires, qui comprend un composé suivant l'une quelconque des revendications précédentes en association avec un support acceptable du point de vue pharmaceutique.

7. Composé suivant l'une quelconque des revendications 1 à 6, destiné à être utilisé en médecine.

8. Utilisation d'un composé suivant l'une quelconque des revendications 1 à 6 pour la préparation d'un médicament destiné à inhiber la lipoxygénase ou la cyclooxygénase.

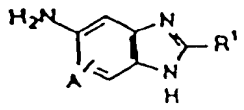
Revendications pour les Etats contractants suivants : GR, ES

1. Procédé de production d'un composé de formule I



et de ses sels pharmaceutiquement acceptables,
formule dans laquelle
R^1 est un groupe -NHR^3, -NR^3(alkyle inférieur) ou R^4 ;
R^2 est un groupe phényle, phényle substitué, naphtyle ou cyclohexyle, les substituants du groupe phényle substitué étant choisis entre des radicaux alkyle inférieur, alkoxy inférieur et halogéno ;
R^3 est un groupe alkyle inférieur, phényle, phényle substitué ou naphtyle ; les substituants du groupe phényle substitué sont choisis dans le groupe comprenant des radicaux alkyle inférieur, alkoxy inférieur et halogéno ;
R^4 est un groupe phényle, phényle substitué, naphtyle ou cyclohexyle ; les substituants du groupe phényle substitué étant choisis dans le groupe comprenant des radicaux alkyle inférieur, alkoxy inférieur et halogéno ;
A est l'hydrogène ou un radical halogéno ; et
m est un nombre entier de 1 à 3,

caractérisé par la réaction d'un composé de formule II



avec un aldéhyde de formule $R^2(CH_2)_{m-1}CHO$

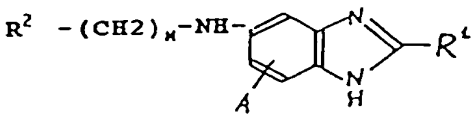
dans laquelle A, R_1, R_2 et m sont tels que définis ci-dessus, suivie de la réduction du produit intermédiaire résultant pour former un composé de formule I, ces opérations étant suivies d'une transformation facultative du produit en un sel pharmaceutiquement acceptable.

2. Procédé suivant la revendication 1, dans lequel la réaction du composé de formule II et de l'aldéhyde a lieu en présence d'un agent déshydratant et le produit intermédiaire résultant est réduit par voie catalytique avec de l'hydrogène ou réduit avec un hydrure métallique.

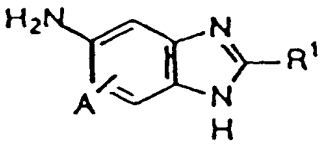
3. Procédé suivant la revendication 2, dans lequel la réaction du composé de formule II et de l'aldéhyde a lieu à une température allant jusqu'à 80 °C et le produit intermédiaire est réduit par voie catalytique avec de l'hydrogène.

4. Procédé suivant la revendication 1, dans lequel on produit
le dichlorhydrate de 5-(3-phénylpropyl)-amino-2-(o-tolyl)-benzimidazole ;
le dichlorhydrate de 2-anilino-5-benzylamino-benzimidazole ;
le dichlorhydrate de 5-benzylamino-2-propylamino-benzimidazole ;
le dichlorhydrate de 5-benzylamino-2-(o-toluidino)-benzimidazole ;
le dichlorhydrate de 5-benzylamino-2-(p-butyl-anilino)-benzimidazole ;
le dichlorhydrate de 5-benzylamino-2-(α-naphtyl)-amino-benzimidazole ; ou
le 2-[(N-méthyl)-anilino]-5-benzylamino-benzimidazole.

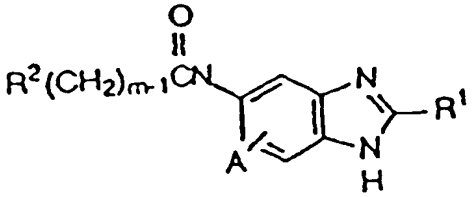
5. Procédé de production d'un composé de formule I



caractérisé par : la réaction d'un amide de formule II



avec un acide activé pour former un composé intermédiaire de formule IV



où A, R_1, R_2 et m sont tels que définis ci-dessus ; et la réduction du composé intermédiaire pour produire un composé de formule I ; ces opérations étant suivies de la transformation facultative du produit en un sel acceptable du point de vue pharmaceutique.

6. Procédé suivant la revendication 5, dans lequel la réaction de l'amide avec l'acide activé a lieu en présence d'une base et le composé intermédiaire est réduit avec un hydrure métallique.

7. Procédé suivant la revendication 6, dans lequel la réaction de l'amide avec l'acide activé est conduite à une température allant de 0 °C à la température de reflux et la réduction est conduite à une température allant de 0 °C à la température de reflux.

8. Procédé suivant la revendication 5, dans lequel on produit
le dichlorhydrate de 5-(3-phénylpropyl)-amino-2-(o-tolyl)-benzimidazole ;
le dichlorhydrate de 2-anilino-5-benzylamino-benzimidazole ;
le dichlorhydrate de 5-benzylamino-2-propylamino-benzimidazole ;
le dichlorhydrate de 5-benzylamino-2-(p-butyl-anilino)-benzimidazole ;
le dichlorhydrate de 5-benzylamino-2-(o-toluidino)-benzimidazole ;
le dichlorhydrate de 5-benzylamino-2-(α-naphtyl)-amino-benzimidazole ; ou
le 2-[(N-méthyl)-anilino]-5-benzylamino-benzimidazole.